# e-Appendix: Methodologic details

## Markov model

A Markov process was used to model the cost and clinical outcomes after percutaneous coronary intervention (PCI) with stenting in 6-month intervals. Fig. 1 is a diagram of the Markov model "tree." A Markov model simulates, on the basis of observed probabilities of transition between discrete clinical states, what would occur over a lifetime in a cohort of patients with the selected treatment. Patients may progress through the following 5 health states after an initial PCI: 1) alive with no clinical restenosis (i.e., event-free), 2) clinical restenosis as determined by the need for a subsequent coronary artery bypass graft (CABG), 3) clinical restenosis as determined by the need for repeat PCI, 4) repeat catheterization with no subsequent revascularization procedure (defined as no PCI or CABG in the ensuing 3 months) and 5) death.

## Meta-analysis

RAVEL[1] (RAndomized study with the sirolimus-eluting VELocity balloon-expandable stent) included 238 patients with unstable and stable angina. SIRIUS[2] (study of the SIRolImUS-eluting stent) had broader inclusion and exclusion criteria and enrolled 1510 patients in the 3 arms. Given that we were interested in the effectiveness of sirolimus-eluting stents, our analysis focused on the reduction in the risk of "clinical restenosis" as determined from repeat procedures undertaken because of symptomatic presentation as opposed to procedures undertaken because of asymptomatic restenosis detected angiographically.

Because all studies included angiography in the protocol, we concluded from the published results that 17 repeat procedures in patients who had received a conventional stent (14.4% restenosis rate) and no repeat procedures in

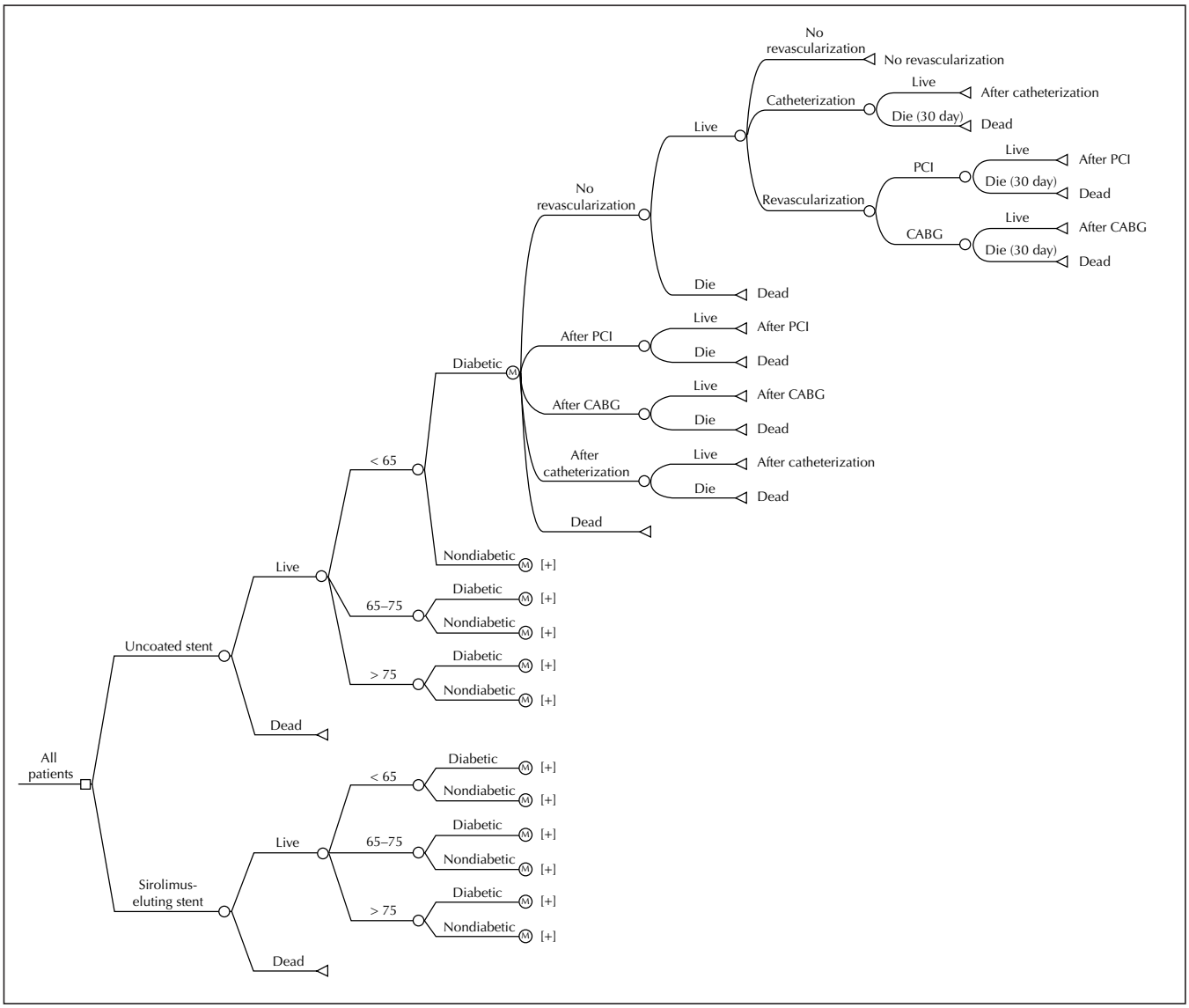


**Fig. 1: Markov model "tree."** PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting.

those who had received a sirolimus-eluting stent were due to clinical restenosis in RAVEL[1] and that 87 repeat procedures in patients who had received a conventional stent (16.6% restenosis rate) and 21 in those who had received a sirolimus-eluting stent (3.9% restenosis rate) were due to clinical restenosis in SIRIUS.[2] C-SIRIUS,[3] the Canadian arm of SIRIUS, reported 9 clinically driven procedures in the conventional stent group (18% restenosis rate) and 3 in the sirolimus-eluting stent group (6% restenosis rate). Similarly, E-SIRIUS,[4] the European arm, reported 40 clinically driven procedures in the conventional stent group (22.6% restenosis rate) and 7 in the sirolimus-eluting stent group (4% restenosis rate).

Data from the 4 trials were pooled with the use of a DerSimonian–Laird random-effects model[5] (Fig. 2) after testing for heterogeneity between the trials with the $\chi^2$ statistic ($p = 0.38$).

## Scenario and sensitivity analyses

To examine the impact of the various assumptions required to run the Markov model, we undertook various scenario and sensitivity analyses. The results were described as "sensitive" if the cost per quality-adjusted life-year (QALY) changed substantially when the estimates were varied within plausible ranges.

The 30-day mortality rates associated with second procedures were varied by ±50% to account for possibly different rates in other centres or countries.[6–8]

To account for practice variations in the preference for use of PCI or CABG to treat clinical restenosis, we varied the probability of receiving CABG, as opposed to PCI, by ±25%.

We also assessed the effect of varying the baseline estimate of the rate of clinical restenosis seen with conventional stents to reflect the restenosis rates reported in the individual trials and in other clinical settings.[1–4] In addition, we varied the clinical restenosis rate by up to 100% to simulate the higher repeat-procedure rate that may be seen among patients with more complex coronary artery lesions.[9] To simulate one of the possible variations in practice patterns, we considered a scenario in which all patients undergoing a second PCI received a sirolimus-eluting stent.

The extent to which the occurrence of repeat catheterization with no subsequent revascularization procedure would be reduced by the use of sirolimus-eluting stents is uncertain. In the baseline analysis, we assumed that only 49.5% of such catheterizations were potentially preventable, and we applied a relative risk of 0.23 for sirolimus-eluting stents. We used 2 scenarios: 1) sirolimus-eluting stents would not prevent such catheterizations (relative risk 1.0); and 2) all such catheterizations were potentially preventable with the use of sirolimus-eluting stents.

In the base case, a health-related quality-of-life (HRQOL) decrement was applied for the first year after the initial PCI. To assess how this assumption affected the results, we evaluated scenarios in which the HRQOL decrement was sustained (i.e., patients with a second procedure maintained the lower HRQOL score for their entire lifetime) or no HRQOL decrement was associated with a procedure. The latter is equivalent to an analysis considering life-years gained instead of QALYs.

We also determined the cost per QALY of sirolimus-eluting stents in patients with different clinical indications for PCI, such as stable or unstable angina, acute myocardial infarction and emergent acute myocardial infarction, by varying the clinical event and the 30-day mortality rates after second procedures that were observed among patients with these indications for the index PCI. We also evaluated the impact of varying the cost of sirolimus-eluting stents by 25% or 50%.

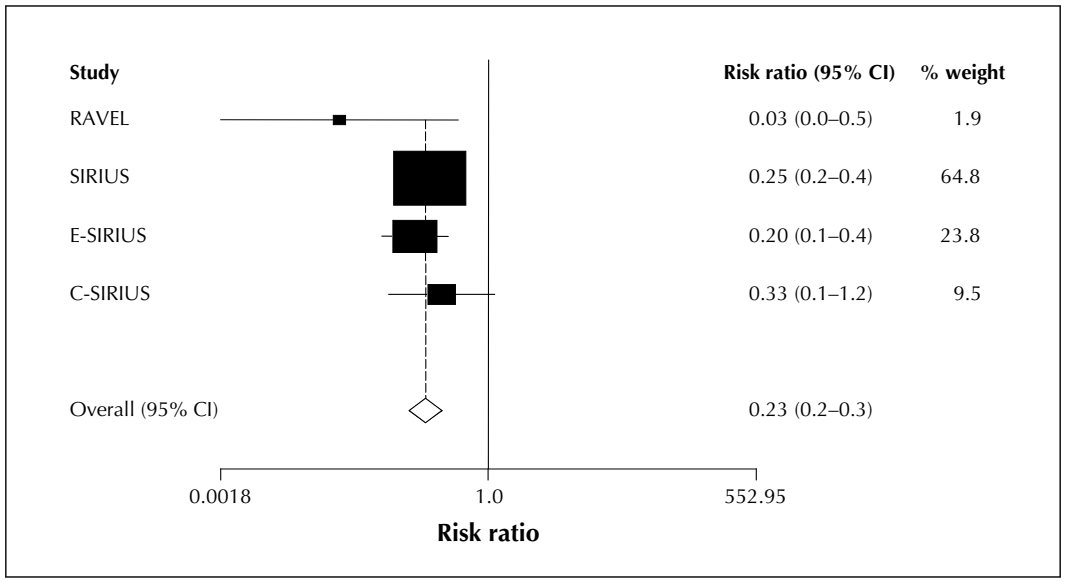


**Fig. 2: Meta-analysis of randomized controlled clinical trials comparing uncoated (conventional) stents and sirolimus-eluting stents.** RAVEL = RAndomized study with the sirolimus-eluting VELocity balloon-expandable stent,[1] SIRIUS = study of the SIRolImUS-eluting stent,[2] E = European arm of SIRIUS,[4] C = Canadian arm of SIRIUS,[3] CI = confidence interval.

Finally, recognizing that our source data for this economic evaluation were obtained from a Canadian cardiac registry, we completed supplementary analyses in which specific assumptions were modified to reflect the US health care situation. Consistent with reports comparing the cost of health care in Canada and in the United States,[10] we increased health care costs by 50%. Restenosis rates were increased to reflect published US estimates and the apparently lower threshold for reintervening with a repeat revascularization procedure after an initial PCI.[11] CABG and PCI 30-day mortality rates were varied to reflect published US estimates.[12,13]

## References


1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773-80.
2. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315-23.
3. Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM, et al, for the C-SIRIUS Investigators. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004;43:1110-5.
4. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, et al; E-SIRIUS investigators. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 2003;362:1093-9.
5. Egger M, Davey Smith G, Altman DG, Chalmers I. *Systematic reviews in health care: meta-analysis in context*. London (UK): BMJ Publishing Group; 2001. p. 347-69.
6. Ghali WA, Quan H, Shrive FM, Hirsch GM, for the Canadian Cardiovascular Outcomes Research Team (CCORT). Outcomes after coronary artery bypass graft surgery in Canada: 1992/93 to 2000/01. *Can J Cardiol* 2003;19:774-81.
7. Jamal SM, Shrive FM, Ghali WA, Knudtson ML, Eisenberg MJ, for the Canadian Cardiovascular Outcomes Research Team (CCORT). In-hospital outcomes after percutaneous coronary intervention in Canada: 1992/93 to 2000/01. *Can J Cardiol* 2003;19:782-9.
8. King SB III, Lembo NJ, Weintraub WS, Kosinski AS, Barnhart HX, Kutner MH, et al. A randomized trial comparing coronary angioplasty with coronary bypass surgery. Emory Angioplasty versus Surgery Trial (EAST) *N Engl J Med* 1994;331:1044-50.
9. Giedd KN, Bergmann SR. Myocardial perfusion imaging following percutaneous coronary intervention: the importance of restenosis, disease progression, and directed reintervention. *J Am Coll Cardiol* 2004;43:328-36.
10. World Bank. *World development indicators 2000*. Washington (DC): The Bank; 2001.
11. Cutlip DE, Chauhan MS, Baim DS, Ho KKL, Popma JJ, Carrozza JP, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol* 2002;40:2082-9.
12. Goodney PP, O'Connor GT, Wennberg DE, Birkmeyer JD. Do hospitals with low mortality rates in coronary artery bypass also perform well in valve replacement? *Ann Thorac Surg* 2003;76:1131-7.
13. Malenka DJ, Wennberg DE, Quinton HA, O'Rourke DJ, McGrath PD, Shubrooks SJ, et al; Northern New England Cardiovascular Disease Study Group. Gender-related changes in practice and outcomes of percutaneous coronary interventions in northern New England from 1994 to 1999. *J Am Coll Cardiol* 2002;40:2092-101.